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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/660,902	SU ET AL.	
	Examiner	Art Unit	
	Angela Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-30 is/are pending in the application.

4a) Of the above claim(s) 27-30 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-26 is/are rejected.

7)☒ Claim(s) 23 is/are objected to.

8)☒ Claim(s) 1-26 are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 12 September 2003 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 3/31/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-26, drawn to methods of determining the sequence of nucleic acids using Raman spectroscopy, classified in class 435, subclass 6.

II. Claims 27-30, drawn to an apparatus with a Raman detector, classified in class 435, subclass 288.7.

The inventions are distinct, each from the other because of the following reasons:

2. Inventions I and II are related as process and apparatus for its practice. The inventions are distinct if it can be shown that either: (1) the process as claimed can be practiced by another materially different apparatus or by hand, or (2) the apparatus as claimed can be used to practice another and materially different process. (MPEP § 806.05(e)). In this case, the process could be practiced using the apparatus of Group II or by hand. Further, the apparatus can be used for any method in which detection is performed with flow through cells, ranging from oligonucleotide synthesis to nucleic acid sequencing to detection by PCR amplification.

3. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

4. Because these inventions are distinct for the reasons given above and the search required for Group I is not required for Group II, restriction for examination purposes as indicated is proper. A search for the methods of Group I would require

terms specific to the method steps such as "exonuclease", "nucleic acid sequencing" and "Raman detection", but would not require terms directed to the specific features of the apparatus of Group II, such as "microfluidic channel", "flow cell" and "reaction chamber".

5. During a telephone conversation with Lisa Haile on December 19, 2005 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-26. Affirmation of this election must be made by applicant in replying to this Office action. Claims 27-30 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

6. Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

7. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Objections

8. Claim 23 is objected to because of the following informalities: a period at the end of the claim is missing. Appropriate correction is required.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 7-21 and 24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

11. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a method of DNA sequencing which involves chemical attachment of nucleotides to nanoparticles as well as biological factors such as enzymatic activities, particularly exonuclease cleavage rates and enzymatic synthesis of multiply labeled nucleic acids. The invention is in a class of invention that the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims encompass any method of sequencing in which nucleotides are sequentially removed from one end of a nucleic acid, whether by exonuclease activity, by polymerase activity or by chemical reactions (paragraph 65 of the specification). The claims further encompass attachment of the released nucleotides to a nanoparticle (paragraph 26 of specification), which can be any of a variety of different molecules ranging from gold beads to nanoprisms (paragraph 46 of specification) with different chemistries, different structures and with a variety of different cross-linking compounds being used (paragraphs 46-51 of specification). Finally, the claims encompass labeling of all four nucleotides of a single DNA molecule with distinguishable Raman labels (see paragraph 25 of specification and claim 24).

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant variability in the activity and reactivity of different cross-linkers and different nanoparticles. Even more importantly, as noted below, the reactivity rates for the cross-linkers are dramatically different than those of the exonuclease. It would require significant and inventive effort to identify crosslinkers that whose rate of binding is sufficiently fast to equal the rate of nuclease cleavage by the exonucleases. Such effort would require synthesis and analysis of a variety of different cross-linkers and sequential analysis of each of these cross-linkers in the nucleotide release assay. The synthesis of novel cross-linkers alone is an inventive effort that would require a substantial amount of time and effort. The further analysis and specific design or screening for a cross-linker with a reaction rate sufficient to function in the exonuclease

sequencing method of claims 7-21 would require substantially more inventive effort than simply finding a novel cross-linker. Finally, with regard to claim 24, inventive effort would be required to find a polymerase that was not subject to the steric hindrances involved in incorporating a full replacement of all four nucleotides with labeled analogues.

The unpredictability of the art and the state of the prior art

The art suggests that the invention cannot work as claimed. Specifically, the reaction rate of the cross-linkers take multiple minutes, while the exonuclease cleavage releases the hundreds of nucleotides every second.

For example, the Nanogold ® particles, cited by Applicant in the specification at page 14, state in their literature (Nanogold ® labeling reagents (http://www.nanoprobes.com/labRgts.html) that the particle must be mixed for hours with the target to obtain the covalent linkage. For example, in the Monomaleimido Nanogold ® section, the literature states "It is easy to use: simply mix redissolved Mnomaleimido Nanogold ® with the target molecule for 1-16 hours." The Mono-sulfo-NHS-Nanogold ® states that "Reaction is complete in a few hours." This reaction rate for the cross-linkers is not limited to the Nanogold ® reagents, since Molecular Probes, in their fact sheet on Thiol-reactive probes, also notes regarding the time for reaction (step 1.6) "Allow the reaction to proceed for 2 hours at room temperature or overnight at 4 C." Thus, the reaction rate for the chemical cross-linkers is measured in minutes.

However, the reaction rate for the exonuclease cleavage of nucleotides from a DNA molecule operates much faster, at a rate of approximately 1000 bases per second (see Matsuura et al, Nucleic Acids Research (2001) 29:e79, abstract). This measurement was performed on a single molecule of DNA, thereby showing the actual

reaction rate of the exonuclease and not the average rate over a variety of molecules. This evidence of Matsuura et al. of rapid rate for exonuclease digestion, combined with the evidence of Nanogold ® and Molecular Probes of a relatively slow rate of cross-linking, suggests that the invention cannot function as claimed. Even if the slower rate used in Sauer et al (J. Biotechnolog. (2001) 86:181-201) is used, with only a cleavage rate of 3-7 nucleotides per second (see page 190, column 1), the time frames do not overlap. The time required for binding of the nanoparticle is significantly longer, by several orders of magnitude, than the time used in exonuclease cleavage. The invention will not function because the released nucleotides will not be able to be sequentially cross-linked and analyzed. Instead, the method will simply crosslink thousands of nucleotides to the nanoparticles, but this bulk reaction will not give sequence information. That is, the order of the nucleotides, the essence of any DNA sequencing operation, will not be preserved for analysis because the cross-linking reagents will be too slow to bind the nucleotides as they are digested. This will result in an absence of order when the particles are subsequently read and no sequence information will be obtained.

A further area of unpredictability concerns claim 24. Sauer et al. expressly teach that "A complete labeling (100% substitution with fluorescent dNTPs) of all four DNA-bases has not yet to be achieved (sic). Steric hindrance at the polymerase active site is supposed to prevent full replacement of natural dNTPs by the modified analogues (see page 188, column 2)." Since the current specification lacks any guidance on how to overcome this art recognized problem, claim 24 is entirely unpredictable since the problem of steric hindrance prevents complete labeling.

Working Examples

The specification teaches the detection of single nucleotide molecules (Example 1), but these nucleotides are not derived from exonuclease-mediated cleavage of a polynucleotide, but rather added to the system and detected. Examples 4 & 6 teach exonuclease-mediated digestion and detection of released nucleotides bound to nanoparticles. However, Examples 4 & 6 are prophetic and given the unpredictable nature of the claimed methods, these examples do not provide the ordinary artisan with nearly enough information to practice the method. As discussed above, significant optimization of reaction parameters such as solution viscosity, temperature, linker choice, and nanoparticle choice would be required in order to obtain an exonuclease cleavage rate that is slower than the rate of nucleotide binding to nanoparticles – a step absolutely essential for practice of the claimed method. Furthermore, with regard to claim 24, the prophetic Example 5 only describes synthesis of a nucleic acid labeled with two different labels, rather than the claimed four different nucleotide labels. As discussed above, labeling of four nucleotides poses serious considerations related to sterics, electrostatics and solubility, and therefore, the person of ordinary skill would need significant guidance in order to practice the claimed method.

Guidance in the Specification

The specification provides no specific or substantial guidance to address the issue of the rate of cross-linking relative to the rate of exonuclease digestion. The specification does generically teach the method, but does not address this specific issue. Although the specification teaches that reaction rates of the exonuclease may be slowed, it is not demonstrated that the rate can be brought within the time scale of

the cross-linking. Given that the rates of digestion and cross-linking vary by an order of magnitude, substantial guidance would be required for the person of ordinary skill to practice the invention. The specification completely lacks guidance on labeling the nucleic acid with all four bases having a distinguishable label beyond assertion of this embodiment of the method.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Therefore, given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art where the cross-linking rates of Nanogold ® and Molecular Probes are significantly slower than the exonuclease rate of Matsuura, the large quantity of research required to define cross-linking reagents that would function in the exonuclease sequencing assay with nanoparticles, the lack of guidance provided in the specification, the absence of any useful working examples balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 1-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

14. Claim 1 recites the limitation "the nucleotides" in step (b). There is insufficient antecedent basis for this limitation in the claim, because step (a) recites "unlabeled nucleotides" making it unclear in step (b) whether "the nucleotides" are the "unlabeled nucleotides" of step (a) or other, perhaps labeled, nucleotides.

Claim 4 is indefinite, because it is unclear whether the phrase "multiple nucleic acid molecules" is meant to refer to multiple copies of the same sequence or multiple nucleic acid molecules, each with a different sequence.

15. Claim 6 recites the limitation "the nucleotides" in line 1. There is insufficient antecedent basis for this limitation in the claim, because the parent claim 1 recites the limitation "the unlabeled nucleotides". As discussed above, claim 1 is indefinite, because it is unclear whether "the nucleotides" are the "unlabeled nucleotides" of step (a) in the method of claim 1 or other (perhaps labeled) nucleotides.

16. Claims 7-21 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: step (c) in the method of claim 7, which appears to be absent. Otherwise, there is a typographical error in the method of claim 7.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 1, 2, 4, and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Kneipp et al. (WO 99/44045).

With regard to claim 1, Kneipp et al. disclose a method comprising:

a) using an exonuclease to release unlabeled nucleotides from one end of one or more nucleic acid molecules (see all of page 15, in particular line 26 where exonuclease is used to remove "fragments" of DNA, line 18 where "each fragment comprises at least one base"; see also page 8, lines 4-9 which state that unlabeled nucleotides are analyzed and that single nucleotides may be detected)

b) separating the nucleotides from the exonuclease and the one or more nucleic acid molecules (page 15, lines 26-30)

c) identifying the unlabeled nucleotides by Raman spectroscopy (page 15, line 30-page 16, line 2 where the "spectral information" is defined on page 14, lines 29-30 as being obtained using Raman spectroscopy)

d) determining the sequence of the nucleic acid from the identified nucleotides (page 15, line 3 and page 15-line 30-page 16, line 2; where determining the identity of

fragments (which comprise nucleotides) in the order in which they are released from a nucleic acid is determining the sequence).

With regard to claim 2, Kneipp et al. disclose the method of claim 1, wherein single molecules of unlabeled nucleotides are identified by Raman spectroscopy (page 8, lines 2-9).

With regard to claim 4, although Kneipp et al. do not specifically teach that "multiple nucleic acid molecules are sequenced simultaneously", this is inherently implied (see page 15). The DNA or RNA sample from which nucleotides are released by exonuclease treatment, absent an explicit statement to the contrary, is inherently comprised of multiple nucleic acid molecules which are being fragmented and sequenced simultaneously. As discussed above, the term "multiple nucleic acid molecules" does not require that the sequence differ within the nucleic acid population. Therefore, the disclosure of Kneipp et al. meets the instant limitation.

With regard to claim 6, Kneipp et al. disclose the method of claim 1, wherein the nucleotides are identified by surface enhanced Raman spectroscopy (SERS) (page 14, lines 29-31).

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

21. Claims 22-23, and 25-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dorre et al. (Bioimaging, 1997) in view of Vo-Dinh (US Patent No. 5,306,403).

With regard to claim 22, Dorre et al. teach a method comprising:

a) obtaining nucleotides that are attached to Raman labels (see 143, column 2, where dUTP and dCTP are attached to TMR and Cy5, respectively, where TMR and Cy5 are both Raman labels),

b) synthesizing a nucleic acid comprising labeled nucleotides (see page 143, column 2),

c) removing nucleotides from one end of the nucleic acid (see page 144, column 1),

d) determining the sequence of the nucleic acid (see page 144, figure 5 and page 145, column 2).

With regard to claim 23, Dorre et al. teach single molecule sequencing (see abstract and title).

With regard to claim 25, Dorre et al. teach attachment of labels only to the pyrimidines, dUTP and dCTP (see page 143, column 2).

With regard to claim 26, Dorre et al. teach synthesis of the DNA fragment to be sequenced by PCR amplification using a template, a primer and a DNA polymerase (see page 143, column 2).

Dorre does not teach detection using Raman spectroscopy, such as SERS.

Vo-Dinh teaches detection of DNA sequencing products using Raman spectroscopy and SERS (see abstract and column 4, lines 16-40).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the Raman spectroscopic method of Vo-Dinh in the sequencing method of Dorre et al. since Dorre et al. state that "A high signal to noise (S/N) ratio is the essence of single molecule detection (see page 145, column 1)." Vo-Dinh answers this requirement for a high signal to noise ratio in detection of DNA sequencing products by the use of Raman spectroscopy, where Vo-Dinh notes "The sensitivity of the Raman spectroscopic component is enhanced by surface enhancement, thus providing a surface enhanced Raman spectroscopy (SERS) system for DNA sequencing (see column 3, lines 30-34)." Further motivation to apply SERS to DNA sequencing is found in column 4, where Vo-Dinh teaches that Raman

spectroscopy has excellent specificity (see column 4, lines 6-9) while the previous problems with SERS are overcome by Vo-Dinh (see column 4, lines 10-15). Thus, an ordinary practitioner would have been motivated to use the SERS detection method of Vo-Dinh to achieve the desired high signal to noise ratio of Dorre et al. in order to enhance the specificity and sensitivity of the DNA sequencing reaction taught by both Dorre et al. and Vo-Dinh.

Claims 3 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kneipp et al. (WO 99/44045) in view of Dorre et al. (Bioimaging, 1997) or Kneipp et al. (Physical Review E, 1998) and further in view of Matsuura et al. (Nucleic Acids Research, August 2001).

Kneipp et al. (WO 99/44045) teach the method of claims 1 and 2, as discussed above.

Kneipp et al. (WO 99/44045) do not explicitly teach sequencing of single nucleotide molecules or attachment of the nucleic acid to a surface.

As discussed above, Dorre et al. teach a single-molecule sequencing method based on the detection of fluorescent nucleotides released by sequential exonuclease digesetion of an immobilized nucleic acid (see abstract and above).

With regard to claim 3, Dorre et al. teach a single-molecule sequencing method (see abstract).

With regard to claim 5, Dorre et al. teach that the nucleic acid is immobilized (see abstract).

Kneipp et al. (Physical Review E, 1998) teach that SERS is capable of detecting unlabeled nucleotides, and therefore, is preferable to fluorescence-based methods of single-molecule sequencing (page 57, column 1, first paragraph).

Matsuura et al. teach that lambda exonuclease digested a single DNA molecule at a rate of 1000 bases/sec (abstract), and reported that this rate was approximately two orders of magnitude faster than a rate of 10 nucleotides/second determined from a population of DNA molecules, where the rate is necessarily an averaged value (page e79, column 2).

It would have been prima facie obvious for one of ordinary skill in the art to conduct the sequencing method of Kneipp et al. (WO 99/44045) using immobilized single nucleic acid molecules as taught by Dorre et al. in order to expand the capability of the method to include sequencing of very long nucleic acids (on the order of tens of kilobases) and also to improve the accuracy of the sequence information obtained. Dorre et al. taught that the sequencing of single fluorescently labeled molecules by exonuclease digestion would greatly increase the sequencing rate, thereby facilitating the sequencing of very long templates (page 139-140). Kneipp et al. in an earlier publication (Physcial Review E, 1998) also recognized the potential for increasing the speed of a sequencing reaction by using a single-molecule method, and noted that SERS detection has the advantage over the fluorescence method of Dorre et al. of not requiring the incorporation of labels into the nucleic acid to be sequenced (page 57, column 1, paragraph 1). Kneipp et al. also reported the detection of a single nucleotide

using SERS (abstract). The combined teachings of Dorre et al. and Kneipp et al. would have provided the ordinary artisan with motivation to use an immobilized single nucleic acid molecule in the method of Kneipp et al. (WO 99/44045) in order to increase the sequencing rate and also accommodate longer templates.

The teachings of Matsuura et al. would have provided even further motivation for performing the sequencing method of Kneipp et al. using a single nucleic acid molecule, because Matsuura et al. reported that the rate of exonuclease digestion could be accurately measured on a single DNA molecule, and that this rate was two orders of magnitude faster (1000 nt/sec vs. 10 nt/sec; see abstract and first page) than the average digestion rate reported for a population of nucleic acids. Since the rate of exonuclease digestion is critical to the method of Kneipp et al. (recall that the metal film to which released nucleotide analytes are adsorbed is moved past the Raman detector at a rate consistent with exonuclease digestion, pages 15-16), the ordinary artisan would have been motivated to use a single nucleic acid molecule in order apply this more accurate estimate of the exonuclease digestion rate and upon adjustment of the detection rate, significantly improve the accuracy of the resulting sequence information. In other words, the teachings of Matsuura et al. are critical to the successful practice of the method of Kneipp et al., because if the exonuclease cleaveage rate is incorrect, the released nucleotides may not be detected in sequential order, and the sequence information obtained would be worthless. Using a single nucleic acid molecule eliminates the possibility of different rates of digestion occurring on different nucleic acid molecules, and greatly improves the accuracy of the resulting sequence information.

Therefore, the preson of ordinary skill, interested in expanding the capability and improving the accuracy of the method of Kneipp et al., would have been motivated to use a single immobilized nucleic acid molecule as taught by Dorre et al. and further suggested by Matsuura et al., thus resulting in the instantly claimed method.

Double Patenting

22. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

23. Claims 22 and 24-26 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 15 and 17-19, respectively, of copending Application No. 11/235,796. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

24. Claims 22 and 24-26 are directed to the same invention as that of claims 15 and 17-19, respectively, of commonly assigned Application No. 11/235,796. The issue of priority under 35 U.S.C. 102(g) and possibly 35 U.S.C. 102(f) of this single invention must be resolved.

Since the U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership

(see MPEP Chapter 2300), the assignee is required to state which entity is the prior inventor of the conflicting subject matter. A terminal disclaimer has no effect in this situation since the basis for refusing more than one patent is priority of invention under 35 U.S.C. 102(f) or (g) and not an extension of monopoly.

Failure to comply with this requirement will result in a holding of abandonment of this application.

25. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 22, 23, 25 and 26 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 3-6 of U.S. Patent No. 6,972,173. Although the conflicting claims are not identical, they are not patentably distinct from each other, because the method the method recited in claim 1 of US Patent No. 6,972,173 constitutes a specific embodiment of the generic method of

the instant claim 22, and therefore, anticipates this claim. The limitation of the instant claim 23 (identification of single nucleotide molecules by Raman spectroscopy) is also encompassed by claims 1, 5 and 6 of US Patent No. 6,972,173, because in exposing only one nucleic acid at a time to exonuclease activity (claim 6 of 6,972,173), sequence determination must depend on the identification of single nucleotide molecules released by sequential exonuclease digestion. The limitations recited in the dependent claims 25 and 26 of the instant application are recited in claims 3 and 4 of US Patent No. 6,972,173.

7. Claims 7, 8, 11-12, and 17-19 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-5, 8, and 11-12 of copending Application No. 11/235,796. Although the conflicting claims are not identical, they are not patentably distinct from each other because the limitations of the instant claims are recited in the conflicting claims of 11/235,796. Specifically, the limitations of the instant claims 7 and 17 are recited in claims 1 and 5 of 11/235,796. The limitation of the instant claim 8 (identification of single nucleotide molecules) is encompassed in claim 11 of 11/235,796 where the identity of each nucleotide is recorded. The limitations of the instant claims 11 and 12 are recited in claims 3 and 4 of 11/235,796, respectively. The limitations of the instant claim 18 are recited in claim 8 of 11/235,796, and the limitations of the instant claim 19 are recited in claim 12 of 11/235,796.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. Claims 7-9, 17-19, and 22-25 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 5, 6, 12, 14, 15 and 18 of copending Application No. 10/108,128. Although the conflicting claims are not identical, they are not patentably distinct from each other, because the method recited in claim 1 of 10/108,128 constitutes a specific embodiment of the generic method recited in the instant claim 7, and therefore, anticipates this claim. The limitation of the instant claim 8 (identification of single nucleotide molecules by Raman spectroscopy) is also encompassed by claims 1, 2 and 5 of 10/108,128, because in immobilizing a single nucleic acid (claim 5 of 10/108,128), sequence determination must depend on the identification of single nucleotide molecules released by sequential exonuclease digestion. The limitation of the instant claim 9 (sequencing of a single nucleic acid molecule) is also recited by claim 5 of 10/108,128. The limitations of the instant claim 18 are recited in claim 1 of 10/108,128. The limitations recited in the instant dependent claims 17 and 19 are recited in claims 6 and 2, respectively of 10/108,128. The method recited in claim 12 of 10/108,128 constitutes a specific embodiment of the generic method of the instant claim 22, and therefore, anticipates this claim. The limitation of the instant claim 23 (identification of single nucleotide molecules) is encompassed in claim 18 of 10/108,128, where the identity of each nucleotide is recorded. The limitations of the instant claims 24 and 25 are recited in claims 14 and 15 of 10/108,128, respectively.

9. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is (571) 272-8291. The examiner can normally be reached on M-F 7:30-5 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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JEFFREY FREDMAN
PRIMARY EXAMINER
2/13/10